antigens. The probability that all resolved fragments in one individual are present in another unrelated individual is estimated at 4×10^{-11} in the case of unrelated father candidates.[1] Our study is in line with these findings. In most paternity cases the combined use of probes 33.6 and 33.15 and one restriction enzyme digestion was sufficient to identify cases of incorrect paternity. It seems even that DNA fingerprints might be highly reliable even for establishing true biological paternity.

The mutation rate of hypervariable minisatellite fragments is low.[2] In our 26 paternity cases we were unable to detect any mutation band in the child. This finding is in agreement with the current low estimates of mutation rate at 0·0038 per DNA fingerprint band per gamete (Jeffreys A, unpublished).

Although DNA fingerprinting as developed by Jeffreys requires only simple manipulations, the process is still labour-intensive and interpretation of bands in the final autoradiographs requires experience. Since the results are far-reaching in human terms, further analyses of this kind are needed to elucidate the practical usefulness and feasibility of DNA fingerprints in paternity testing.

This study was supported by grants from the Finnish Academy and the Sigrid Juselius Foundation. We thank Dr Kimmo Aho for useful comments. The minisatellite probes 33.6 and 33.15 are the subject of patent applications filed in the name of The Lister Institute of Preventive Medicine. ICI plc are the exclusive licensees under these patent applications and all commercial inquiries regarding the probes and their use should be addressed to ICI Diagnostics Group, Gadbrook Park, Rudheath, Northwich, Cheshire CW9 7RA, UK.

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Therapeutics

MANAGEMENT OF DYSPEPSIA: REPORT OF A WORKING PARTY*

A GROUP of ten gastroenterologists, with differing backgrounds and divergent views, met at the time of the American Gastroenterology Association meeting in Chicago, in an attempt to suggest a practical approach to the management of dyspepsia.

Dyspepsia may be an early symptom of a serious illness, such as peptic ulceration, cholelithiasis, or gastric carcinoma, but often no organic lesion is found.[1,2] Dyspepsia has considerable implications for individual suffering, medical workload, and financial cost. Nearly half of gastroenterological practice involves the management of patients in whom no organic lesion can be identified:[3] many have dyspepsia. The majority are treated in general practice. No agreement has yet been reached on the definition, classification, or management of dyspepsia.[4-6] Even the term dyspepsia is not universally understood—W. Grant Thompson[7] commented that "dyspepsia defies definition".

The social and economic implications of dyspepsia have been studied in Sweden, where the cost of outpatient care and drugs for dyspepsia was estimated at £26 million (US $47 million) for a population of about 8 million people. When the cost of loss of earnings and sick-leave benefit was taken into account, the annual cost was estimated as about £280 million.[8]

Medical decisions should not be based primarily on cost, but financial considerations are becoming increasingly important. Careful selection of patients for investigation is, therefore, essential. Factors pointing to organic disease should be linked with the symptoms to place the patient into a defined category, so that the most appropriate management may be offered. A trial of therapy, without investigation, is suggested where the features in a younger patient do not suggest an organic cause. However, no trial of therapy should be prolonged: if it fails, investigation is required.

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Other members of the working party: Dr B. Bloom (Philadelphia); Dr G. Bodemar (Linkoping); Dr G. Crean (Glasgow); Prof J. Freston (Farmington); Prof R. Gugler (Bonn); Prof J. Malagelada (Barcelona); Dr O. Nyrén (Uppsala); Prof H. Petersen (Trondheim); Prof D. Piper (Sydney).

DEFINITIONS

We defined *dyspepsia* as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptom considered to be referable to the proximal alimentary tract. This broad definition includes the whole range of symptomatic upper gastrointestinal disease. Management of patients with dyspeptic symptoms must aim to identify, investigate, and treat those most likely to have an organic illness, and to identify and treat those in whom organic lesions are unlikely. We used the term non-ulcer dyspepsia to describe the symptoms of patients in the latter group. *Non-ulcer dyspepsia* was defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptom considered to be referable to the proximal alimentary tract, and lasting for more than 4 weeks, unrelated to exercise, and for which no focal lesion or systemic disease can be found responsible. *Organic dyspepsia* was defined as dyspepsia due to specific lesions—such as peptic ulcer, reflux oesophagitis, gastric carcinoma, and cholelithiasis—which could be readily identified on routine investigation.

CATEGORIES OF NON-ULCER DYSPEPSIA

It is possible to divide patients with dyspeptic symptoms into a number of groups, based largely on symptoms which suggest, albeit imperfectly, causative factors.

Gastro-oesophageal Reflux-like Dyspepsia: gastro-oesophageal reflux is not usually difficult to diagnose from

SYMPTOMS SUGGESTING NON-ULCER DYSPEPSIA

General
- Patient remains well
- Weight steady
- A "worrier"

Reflux-like
- Retrosternal discomfort especially
  - on stooping
  - after large meals
  - on lying flat
- Burning retrosternal discomfort: temporary relief from antacids
- Severity is cyclical
- Recent weight gain

Dysmotility
- Abdominal distension
- Hungry but premature satiety
- Epigastric heaviness or fullness
- Variable and multiple food intolerances
- Pain is diffuse—often several pains—not at night
- Nausea prominent
- Associated features of the irritable bowel
- If vomits, "cannot face food"
- Not episodic—tends to be continuous

the history, but there may be no differences in symptom type, frequency, or severity between patients with focal lesions on endoscopy, and those without (see table). The symptoms are typical—substernal or epigastric discomfort and heartburn; a burning upper epigastric pain; and regurgitation of acid or, occasionally, food. Meals, drinking hot liquids, or change of posture may aggravate these complaints. (Rumination is an uncommon condition whose symptoms superficially resemble gastro-oesophageal reflux, but is a voluntary process. It is characterised by regurgitation of a small amount of food—usually of one mouthful at a time—which is then re-chewed and swallowed. This is always postprandial, and not affected by posture. Manometric studies may be helpful in difficult cases.[9])

Dysmotility-like Dyspepsia: this overlaps with the irritable bowel syndrome and is associated with a feeling of flatulence, bloating and distension, meteorism, and early satiety. Patients tend to feel hungry, and yet are abnormally full after consuming only a small proportion of a meal. Nausea is common, especially first thing in the morning, and may be associated with retching (table). Manning et al's criteria are valuable in distinguishing patients with true irritable bowel syndrome:[10] the four symptoms most closely associated with irritable bowel syndrome are abdominal distension; more frequent stools with the onset of pain; pain eased after bowel movement; and looser stools at the onset of pain. Nearly two-thirds of these patients have at least three of the four symptoms. Alternating diarrhoea and constipation,[11] the passage of mucus, and a sensation of incomplete evacuation are also features of the irritable bowel syndrome.

Ulcer-like Dyspepsia: a small group of patients have symptoms suggestive of an ulcer—being woken by pain at night; getting pain relief from eating small meals or antacid; episodic pain; using one or two fingers to point to localised epigastric discomfort—and yet no ulcer is found. It has been suggested that this represents one end of the spectrum of ulcer disease.[12] (Patients with a history of proven ulcer disease, whether or not an ulcer crater is evident, are excluded: they are presumed to have a symptomatic recurrence of their ulcer disease.)

Aerophagia: varies from an exaggeration of normal swallowing to an abnormal technique of swallowing in which the upper oesophageal sphincter relaxes with the glottis closed, so that air is sucked in by negative intrathoracic pressure. Aerophagia is most frequently postprandial and may be related to stress. Typical features include repetitive belching or bloating, frequent dry swallows and gulping, and a characteristic forward movement of the neck when swallowing. Patients with aerophagia rarely obtain relief from belching, and the belching is almost invariably repetitive.

Idiopathic, or Essential, Dyspepsia: about 25% of patients with non-ulcer dyspepsia do not fit into the groups indicated above. They have no specific features on history or examination; we suggest that this group should be called idiopathic dyspepsia. In the future, this group may be subdivided as new information becomes available.

PATHOPHYSIOLOGY

The causes of dyspepsia remain poorly understood. Furthermore, if an abnormality is found, it is not necessarily the cause of the patient's distress. In a dyspeptic patient who is found to have gallstones, for instance, the gallstones may be unrelated to the patient's symptoms.

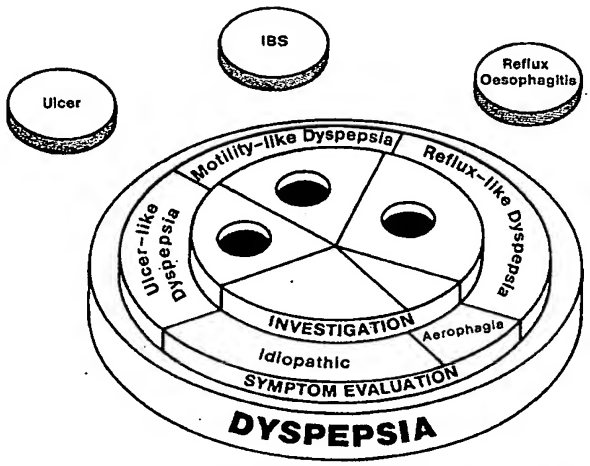
Gastric Acid Secretion: several studies have failed to show any consistent difference between the basal acid output, peak acid output, or gastric secretion in response to stimuli between dyspeptic patients and normal controls.[13] 24-hour pH monitoring in patients with symptoms, but with no oesophagitis at endoscopy, has shown a correlation between symptoms and reflux of acid.

Gastritis and Duodenitis: Siurala et al[14] and Villako et al[15] investigated representative samples of the population, and found prevalence rates of gastritis similar to those reported in dyspeptics. These findings have been supported by endoscopic biopsy.[16] More recently, it has been shown that there are more polymorphonuclear leucocytes in biopsy specimens from dyspeptic patients,[17] suggesting the possibility of infection. Gastric erosions may be found in the normal symptomless population, but may be more common in non-ulcer dyspepsia.[18] Duodenitis may be a cause of ulcer-like dyspepsia,[19] but, especially if there are erosive changes, it is probably a component of duodenal ulcer disease.[20]

Campylobacter pylori: acute infection with *Campylobacter pylori* may cause dyspepsia, which seems to be short-lived.[21] There is now good evidence of an association between *Campylobacter* infection and chronic gastritis, but whether chronic *Campylobacter* infection causes symptoms remains uncertain.[22] Correlation between chronic non-autoimmune gastritis and symptoms is very poor, but some studies indicate that eradication of the organism by bismuth may improve the histological changes and, sometimes, the symptoms.[23]

Motility: motility studies have shown that approximately half the patients with dyspeptic symptoms of unknown origin have some delay in gastric emptying, with antral hypomotility.[24] Under stress, normal antral motility may change to hypomotility in some patients.[25]

Food Allergy: the lay public attributes dyspepsia to food or drink, but critical evaluation has shown that food intolerance and allergy are responsible for symptoms in few patients. These are usually atopic, develop overt features of allergy such as urticaria, and do so reproducibly to specific items of food.[26,27] Dyspeptic sufferers have a greater number of foods to which they have an aversion than control or ulcer patients.



Schematic diagram to represent the clinical problem called dyspepsia (outer circle), within which some will present to their doctor (middle circle) and be grouped according to their symptoms. The investigation of some (inner circle) will reveal specific diagnoses (discs) thereby removing them from the bulk of dyspeptic patients.

Duodeno-gastric Reflux: reflux of duodenal contents, especially bile, has been implicated in some patients with dyspepsia, and may reflect a motility disorder, but the evidence for such effects is not yet convincing.[28]

Psychological Factors: data from Australia suggest that major life events are not strikingly more common in dyspeptic patients than in controls,[29] but they appear to be slightly more neurotic.[30] Unlike ulcer patients, whose absence from work is mainly due to abdominal complaints, patients with dyspepsia of unknown cause report various symptoms, dominated by musculo-skeletal pains;[31] they also tend to have a low pain threshold. These patients may have a heightened perception of physiological function, but this aspect is very difficult to evaluate because of uncontrollable factors, such as ethnic and cultural differences.

INVESTIGATION AND DIAGNOSIS

The term non-ulcer dyspepsia implies that investigation is always needed to exclude focal disease. We believe this policy is correct for anyone over the age of about 45 years—especially if the dyspepsia is of recent origin—as there is a higher frequency of organic disease in this group of patients. In younger patients, the prevalence of organic disease is lower.[32] The symptoms discussed above should be actively sought in the interview (see table and figure) and if they are mild, infrequent, or fall into one of the defined categories, then careful explanation, reassurance, and possibly a trial of therapy, is suggested for the younger patient. Investigation should follow if there is no response, or if there is a swift recurrence. Features pointing towards organic disease, especially in smokers, require early investigation. In general, multiple invasive tests are not required, or appropriate, in patients with dyspepsia. A careful history and limited investigation are all that are normally needed, but physicians must ask about specific symptoms. Endoscopy will normally be the investigation of first choice, because of its ability to detect mucosal lesions more accurately than radiological contrast studies. If endoscopy is unhelpful, an ultrasound examination of the gallbladder and pancreas should be considered. Recently, newer techniques have become available which may be helpful. 24-hour intraoesophageal pH monitoring is indicated particularly in reflux-like dyspepsia, when it may show increased acid reflux, despite the absence of a focal lesion.[33] The Bernstein oesophageal acid perfusion test seems to be unhelpful; and there is no place for assessment of gastric acid secretion in dyspeptic patients. Gastric emptying studies are useful, and are best done by radioisotope methods as they are non-invasive. Gastrointestinal motility studies provide valuable data,[24] but are not yet widely available. If the symptoms persist, other diagnoses should be considered, particularly in older patients.

TREATMENT

There is a natural tendency for non-ulcer dyspepsia to improve,[34] and a large placebo response in this group of patients makes evaluation of different treatments difficult. Patients should be given general advice, an explanation of their symptoms, and firm reassurance. When necessary, patients should be counselled about risk factors thought to be contributing to their symptoms. No specific medication, drug, or group of drugs appears effective in all patients with dyspepsia. We suggest the following management for these different groups of patients.

Gastro-oesophageal Reflux-like Dyspepsia: patients with reflux-like symptoms will usually respond to the same lifestyle modifications recommended for treatment of established reflux oesophagitis, such as elevation of the head of the bed and weight loss. Smoking, excessive caffeine or chocolate, and anticholinergic drugs should be avoided. Patients with reflux-like dyspepsia respond to treatment with cimetidine,[35,36] so a trial of H_2-receptor antagonist therapy could be beneficial. Some patients find antacids helpful.[37]

Dysmotility-like Dyspepsia: drugs such as metoclopramide or domperidone may help.[38] Cisapride is not yet available, but preliminary results are encouraging.

Ulcer-like Dyspepsia: H_2-receptor antagonists may be effective in patients with ulcer-like dyspepsia,[39] as recent studies have shown the efficacy of cimetidine in these patients.[40,41] However, another study which grouped all non-ulcer dyspepsia patients together failed to show benefit from treatment with either antacid or cimetidine.[42]

Aerophagia: there is no specific therapy for patients who swallow air and they are all difficult to treat. Diversion of attention after a meal—which is a common time for such people to swallow air—is often helpful, as is sucking sweets, or sipping drinks. An underlying depressive illness, which might respond to specific therapy, should be excluded.

Idiopathic, or Essential, Dyspepsia: no treatment has been clearly shown to help these patients. Counselling and reassurance is beneficial in some cases. Several drugs have been tried for relief of symptoms—including antacids, bismuth, anticholinergics, and H_2-receptor antagonists—but there is limited evidence of their efficacy. Clinical trials in this area are needed.

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Hospital Practice

BALANCING COST AND BENEFIT IN TREATMENT OF LATE CANCER

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DEVELOPED nations overall have failed to moderate the spiralling expenditure on high-technology medical investigation and treatment. In the absence of open public and political discussion on how best to ration scarce resources, a short-term solution can be achieved by health professionals. In the case of cancer management, physicians can regulate their expenditure by clinical budgeting and by selecting treatment which is clinically appropriate for each individual patient.

As resources are limited, it is no longer justifiable for one physician to spend twice as much money as another on treating patients with similar diseases. The leaders of the profession in the UK have accepted the need for instruction of physicians on the relative values of different procedures for clinical investigation and treatment. Leading medical journals in Britain have begun to point out that "doctors will need to . . . integrate costs into clinical decision making",[1] and that "the separation of clinical judgment from financial responsibility will soon end".[2]

GUIDELINES FOR SELF-REGULATION

Physicians need specific guidelines to enable them to decide whether or not to admit a patient to hospital, to order a test, or to provide ancillary help.[3] These guidelines must be based on objective criteria and should not be regarded by the physician as a threat to his autonomy. The incentive will be that avoidance of inappropriate spending will improve the quality of care for those patients for whom treatment is appropriate. The principles described below must be observed if self-regulation is to be successfully applied by physicians in the treatment of the patient with advanced cancer. (The tiny proportion of patients in approved clinical trials are, however, excluded from discussion.)

The first step in monitoring costs is for administrators and health economists to analyse costs and suggest ways of reducing waste. One controversial approach is the system, developed at Yale University, of diagnosis-related groups, with a range of tests, treatment, and hospital stay appropriate to each. It allows comparison of cost-efficiency between one hospital and another, so that institutions with abnormally low or high costs can be identified. The system does not, however, monitor the quality of treatment received, and it ignores the social needs of patients, and so it should not be regarded as a directive to physicians.

The second solution to cost restraint in cancer treatment is a system in which priority is decided by the needs and likely benefit of the patient. For the physician, the treatment decision should be influenced not by any conscious wish to keep down the overall costs of his organisation but only by a realistic assessment of risk-benefit and cost-benefit ratios in the case of each patient. Clinicians must also be responsible for ensuring both high-quality treatment and the patient's satisfaction with the services provided.

Only clinicians can both ensure that patients receive a share of resources commensurate with their needs and at the

Rome II

Functional gastroduodenal disorders

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Abstract

While widely used in research, the 1991 Rome criteria for the gastroduodenal disorders, especially symptom subgroups in dyspepsia, remain contentious. After a comprehensive literature search, a consensus-based approach was applied, supplemented by input from international experts who reviewed the report. Three functional gastroduodenal disorders are defined. Functional dyspepsia is persistent or recurrent pain or discomfort centered in the upper abdomen; evidence of organic disease likely to explain the symptoms is absent, including at upper endoscopy. Discomfort refers to a subjective, negative feeling that may be characterized by or associated with a number of non-painful symptoms including upper abdominal fullness, early satiety, bloating, or nausea. A dyspepsia subgroup classification is proposed for research purposes, based on the predominant (most bothersome) symptom: (*a*) ulcer-like dyspepsia when pain (from mild to severe) is the predominant symptom, and (*b*) dysmotility-like dyspepsia when discomfort (not pain) is the predominant symptom. This classification is supported by recent evidence suggesting that predominant symptoms, but not symptom clusters, identify subgroups with distinct underlying pathophysiological disturbances and responses to treatment. Aerophagia is an unusual complaint characterized by air swallowing that is objectively observed and troublesome repetitive belching. Functional vomiting refers to frequent episodes of recurrent vomiting that is not self-induced nor medication induced, and occurs in the absence of eating disorders, major psychiatric diseases, abnormalities in the gut or central nervous system, or metabolic diseases that can explain the symptom. The current classification requires careful validation but the criteria should be of value in future research.

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Keywords: dyspepsia; functional dyspepsia; aerophagia; psychogenic vomiting; Rome II

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Based on the consensus opinion of an international panel of clinical investigators who reviewed the available evidence, a classification of the functional gastroduodenal disorders (category B) into functional dyspepsia (category B1), aerophagia (category B2), and functional vomiting (category B3) is recommended (table 1). In addition, symptom subgroups for functional dyspepsia are proposed, namely ulcer-like dyspepsia (B1a) and dysmotility-like dyspepsia (B1b), based on patient ranking of the most bothersome complaint. The evidence in support of this classification is summarized here, and an approach to management reviewed.

Table 1 Functional gastrointestinal disorders

A. Esophageal disorders
- A1. Globus
- A2. Rumination syndrome
- A3. Functional chest pain of presumed esophageal origin
- A4. Functional heartburn
- A5. Functional dysphagia
- A6. Unspecified functional esophageal disorder

B. Gastroduodenal disorders
- B1. Functional dyspepsia
  - B1a. Ulcer-like dyspepsia
  - B1b. Dysmotility-like dyspepsia
  - B1c. Unspecified (non-specific) dyspepsia
- B2. Aerophagia
- B3. Functional vomiting

C. Bowel disorders
- C1. Irritable bowel syndrome
- C2. Functional abdominal bloating
- C3. Functional constipation
- C4. Functional diarrhea
- C5. Unspecified functional bowel disorder

D. Functional abdominal pain
- D1. Functional abdominal pain syndrome
- D2. Unspecified functional abdominal pain

E. Biliary disorders
- E1. Gall bladder dysfunction
- E2. Sphincter of Oddi dysfunction

F. Anorectal disorders
- F1. Functional fecal incontinence
- F2. Functional anorectal pain
  - F2a. Levator ani syndrome
  - F2b. Proctalgia fugax
- F3. Pelvic floor dyssynergia

G. Functional pediatric disorders
- G1. Vomiting
  - G1a. Infant regurgitation
  - G1b. Infant rumination syndrome
  - G1c. Cyclic vomiting syndrome
- G2. Abdominal pain
  - G2a. Functional dyspepsia
  - G2b. Irritable bowel syndrome
  - G2c. Functional abdominal pain
  - G2d. Abdominal migraine
  - G2e. Aerophagia
- G3. Functional diarrhea
- G4. Disorders of defecation
  - G4a. Infant dyschezia
  - G4b. Functional constipation
  - G4c. Functional fecal retention
  - G4d. Non-retentive fecal soiling

B1. Functional dyspepsia

DEFINITION

Although many definitions have been proposed, the committee, following a review of the literature, endorsed the original Rome definition.[1] Hence, dyspepsia refers to pain or discomfort centered in the upper abdomen.

Centered implies that the pain or discomfort is mainly in or around the midline. Pain in the right or left hypochondrium is not considered to be representative of dyspepsia. Discomfort

Abbreviations used in this paper: GERD, gastro-esophageal reflux disease; IBS, irritable bowel syndrome; EGG, electrogastrography.

Table 2 The spectrum of dyspepsia symptoms and recommended definitions

Symptom	*Definition*
Pain centered in the upper abdomen	Pain refers to a subjective, unpleasant sensation; some patients may feel that tissue damage is occurring. Other symptoms may be extremely bothersome without being interpreted by the patient as pain. By questioning the patient, pain should be distinguished from discomfort.
Discomfort centered in the upper abdomen	A subjective, unpleasant sensation or feeling that is not interpreted as pain according to the patient and which, if fully assessed, can include any of the symptoms below.
Early satiety	A feeling that the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal being eaten, so that the meal cannot be finished.
Fullness	An unpleasant sensation like the persistence of food in the stomach; this may or may not occur postprandially (slow digestion).
Bloating in the upper abdomen	A tightness located in the upper abdomen; it should be distinguished from visible abdominal distension
Nausea	Queasiness or sick sensation; a feeling of the need to vomit

refers to a subjective, negative feeling that the patient does not interpret as pain and which, if fully assessed, can include a number of specific symptoms. Discomfort may be characterized by or associated with upper abdominal fullness, early satiety, bloating, or nausea; these symptoms typically are accompanied by a component of upper abdominal distress (table 2).

Duration is not specified as part of the definition because patients may present immediately following the onset of symptoms or may wait months or years before being evaluated. In research studies, investigators may opt for a specified duration of symptoms to define dyspepsia (e.g., two, four, or 12 weeks), and this should depend on the study setting and objectives so as to improve homogeneity of the patients being studied. The painful or uncomfortable symptoms may be intermittent or continuous, and may or may not be related to meals.

There is growing consensus based on 24 hour esophageal pH testing that patients with a history of typical heartburn, when this is a dominant complaint, have symptomatic gastroesophageal reflux disease (GERD), until proved otherwise.[2] There is reasonably good evidence that predominant heartburn is sensitive and specific for GERD, and hence the positive predictive value for heartburn is high in countries where GERD is a common disease.[3] How many patients with burning epigastric pain alone truly have GERD is unknown.

Uninvestigated versus investigated dyspepsia

It is important to distinguish the patient who presents with dyspepsia that has not been investigated (uninvestigated dyspepsia) from patients with a diagnostic label after investigation, with either a structural diagnosis (such as peptic ulcer or GERD), or functional dyspepsia (fig 1).

Causes of dyspepsia

From an etiological viewpoint, patients with dyspepsia can be subdivided into three main categories[1]:

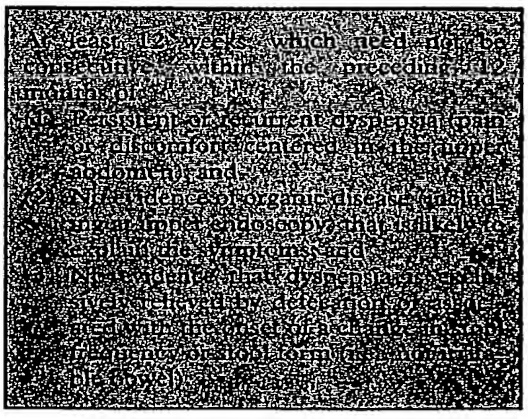
(1) those with an identified cause for the symptoms (e.g., chronic peptic ulcer disease, gastroesophageal reflux disease with or without esophagitis, malignancy, pancreatico-biliary disease, and medications);
(2) those with an identifiable pathophysiological or microbiologic abnormality of uncertain clinical relevance (e.g., *Helicobacter pylori* gastritis, histologic duodenitis, gallstones, visceral hypersensitivity, gastroduodenal dysmotility); and
(3) those with no identifiable explanation for the symptoms.

It is those patients who have no definite structural or biochemical explanation for their symptoms (i.e., categories 2 and 3) that are considered to have functional dyspepsia. The term non-ulcer dyspepsia remains in popular usage, but is not recommended here because some patients with functional dyspepsia will have symptoms not at all like an ulcer, and peptic ulcer is not the only disease of exclusion in patients with dyspepsia.[4]

DIAGNOSTIC CRITERIA

Functional dyspepsia

Symptom patterns alone are unable to adequately discriminate organic from functional dyspepsia.[4 5] Patients need to have been investigated to rule out relevant organic disease. Functional dyspepsia therefore remains a diagnosis of exclusion. There is agreement that symptoms should have run a chronic course before a patient is labeled as having functional dyspepsia. It is therefore recommended that functional dyspepsia be defined as follows:



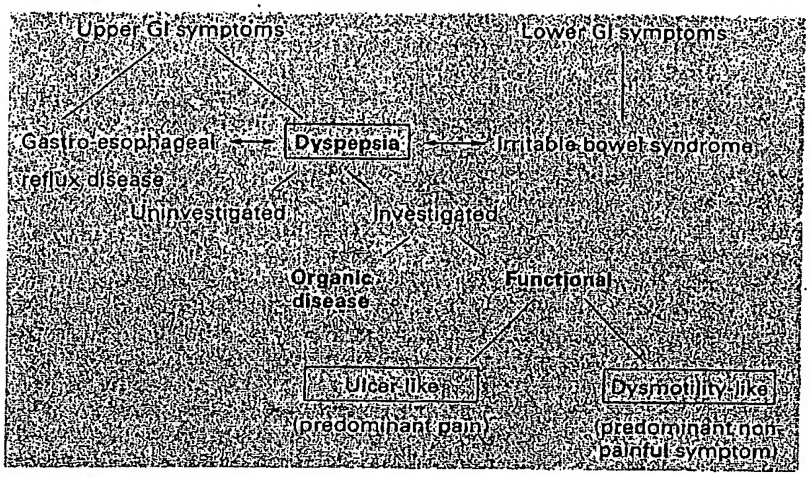


Figure 1 Relationship between dyspepsia and functional dyspepsia. GI, gastrointestinal.

The minimum diagnostic workup required to sustain a diagnosis of functional dyspepsia in the research context is a careful history and physical examination, and an upper endoscopy during a symptomatic period off antisecretory therapy. In the research setting, additional investigations depend on the research question.

Patients with a past history of documented chronic peptic ulcer disease should generally not be classified as having functional dyspepsia. However, patients who have had ulcer disease cured by *H pylori* eradication may remain symptomatic[6]; a subset of these patients probably has functional dyspepsia although this remains poorly documented.

Functional dyspepsia subgroups

The concept of subdividing dyspepsia into subsets based on distinctive symptom patterns continues to be controversial, but has become entrenched in clinical practice.[7] Four working teams have independently proposed that functional dyspepsia be subdivided into symptom subgroups,[1 8-10] but the definitions of the subgroups have not been uniform. In contrast to other groups, the previous Rome criteria proposed not to include the reflux-like subgroup in functional dyspepsia as these patients have GERD until proved otherwise.[1] Two main hypothetical subgroups were identified in all the reports: ulcer-like and dysmotility-like dyspepsia, characterized respectively by aspects of pain, or by symptoms distinct from pain and suggestive of impaired gastroduodenal motility. Two working team reports introduced numeric limitations by requiring the concomitant presence of at least two[9] or three[1] specific symptoms to be included in a subgroup, thus arbitrarily introducing the concept of symptom clusters.

Epidemiologic, pathophysiologic, and clinical studies over the past five years, have demonstrated that the symptom cluster classification is of no clinical utility.[4 11] The dyspepsia subgroup classification proposed here is therefore based not on symptom clusters but on the predominant (or most bothersome) single symptom identified by the patient as defined below:

B1a. *Ulcer-like dyspepsia*

> Pain centered in the upper abdomen is the predominant (most bothersome) symptom.

B1b. *Dysmotility-like dyspepsia*

> An unpleasant or troublesome non-painful sensation (discomfort) centered in the upper abdomen is the predominant symptom; this sensation may be characterized by, or associated with upper abdominal fullness, early satiety, bloating, or nausea.

Recent studies support the existence of such subgroups, as defined by the presence of a predominant (or most bothersome) single symptom identified by the patient. Stanghellini *et al* showed that female gender, postprandial fullness severe enough to influence usual activities, and vomiting severe enough to change usual activities were independently associated with delayed gastric emptying, but clusters of symptoms were not associated.[12] Tack *et al* observed that early satiety was specifically linked to impaired gastric accommodation.[13] The response to proton pump inhibitor therapy in two large trials was linked to subgrouping based on the most bothersome symptom (those with epigastric pain but not discomfort had a statistically significant response to omeprazole over placebo), but this was not observed using the approach of symptom clusters.[14] Although not all studies agree,[15] the proposed subgroups represent a reasonable working hypothesis, although they must be subjected to further careful validation.

B1c. *Unspecified (non-specific) dyspepsia*

> Symptomatic patients whose symptoms do not fulfil the criteria for ulcer-like or dysmotility-like dyspepsia.

Overlap syndromes

Heartburn—Patients in whom heartburn (i.e., burning retrosternal pain) is the predominant symptom are excluded from dyspepsia by definition and almost invariably have GERD.[2 4] However, patients with functional dyspepsia very often have heartburn as an additional symptom subordinate to their abdominal pain or discomfort. In many of these cases the heartburn is so minor or infrequent that it cannot be considered abnormal. A minority of others with frequent heartburn, if fully investigated, are found to have pathological acid reflux on ambulatory esophageal pH monitoring; they have GERD and their inclusion in functional dyspepsia is then recognized to be mistaken.[16]

Irritable bowel syndrome—Dyspepsia occurs commonly in patients with symptoms otherwise compatible with irritable bowel syndrome (IBS).[17] Despite this overlap, most patients

with functional dyspepsia do not have significant bowel symptoms if strict definitions are applied,[17] and dyspepsia is likely to comprise a distinct syndrome based on factor analysis studies.[18] However, it is possible for individuals to have both functional dyspepsia and IBS, or have upper abdominal pain or discomfort exclusively related to IBS. Therefore, if upper abdominal pain or discomfort is exclusively relieved by defecation and/or is associated with a change in bowel pattern, IBS is the diagnosis by definition. On the other hand, if there is pain or discomfort in the upper abdomen that is unrelated to bowel pattern and there is other pain or discomfort that is related to bowel pattern, then functional dyspepsia and IBS can be considered to coexist.

RATIONALE FOR CHANGES IN DIAGNOSTIC CRITERIA

The definition of functional dyspepsia is essentially unchanged. It was, however, not felt to be useful to restrict the definition arbitrarily to a set number of days over a three month period in research or practice, and thus this part was deleted. Although patients with predominant heartburn are excluded from the functional dyspepsia category, patients with IBS are not in the new classification. The definitions of the dyspepsia subgroups have been altered based on clinical, epidemiological, and therapeutic evidence that the original concept of symptom clusters are of no value. In contrast, a classification applying the predominant symptom may identify distinct groupings.[12–14] This approach, however, still requires careful validation.

CLINICAL EVALUATION

The management of the patient with uninvestigated dyspepsia should not be confused with the approach to the patient with documented functional dyspepsia.

Uninvestigated dyspepsia

The current best test for excluding structural causes of dyspepsia is upper endoscopy.[4] However, there is growing consensus that *H pylori* testing is a useful approach for managing new patients.[4 19] Among those with uninvestigated dyspepsia who are *H pylori* positive, a substantial number will have peptic ulcer disease.[20] Endoscopy can now generally be reserved for patients who present with symptoms for the first time in older age or who have alarm features such as weight loss, vomiting, dysphagia, or bleeding that strongly suggest structural disease may be present.[4]

Functional dyspepsia

Performance of an upper endoscopy during a symptomatic period off acid suppressant therapy is essential to identify functional dyspepsia appropriately by excluding other important structural diseases. Ultrasonography is not recommended as a routine clinical test, as in outpatient studies most patients have no detectable abnormality in the absence of symptoms or biochemical tests suggestive of biliary tract or pancreatic disease.[21] Barium radiography of the small bowel is useful if there is any suspicion of mechanical obstruction.

A gastric emptying study (e.g., scintigraphy) is not currently recommended as a routine clinical test. Indeed, there is no convincing evidence that prokinetics are more efficacious in those patients with functional dyspepsia who have delayed versus normal gastric emptying,[22] although conflicting results have been published.[23] In patients with resistant symptoms, a gastric emptying test may be considered. If gastroparesis is found on a gastric emptying study, then specific causes of gastroparesis need to be excluded, and in particular, intestinal obstruction, diabetes mellitus, connective tissue disease, and drugs. Gastroduodenal manometry and electrogastrography (EGG) provide objective evidence of neuromuscular dysfunction in selected patients, and their role in clinical medicine is evolving at this time.

Patients with chronic or severe symptoms may benefit from an appropriate psychiatric history being taken to exclude depression, somatoform disorder, and an eating disorder.

TREATMENT

The range of therapies prescribed for functional dyspepsia reflects the uncertain pathogenesis and the lack of satisfactory treatment options. Management is further confounded by high placebo response rates: between 20 and 60% of patients with functional dyspepsia have symptom improvement on placebo.[24 25] Drug therapy is not always required: a proportion of patients will respond satisfactorily to reassurance and explanation.

Anecdotally, dyspeptic symptoms may be lessened by avoiding offending foods, a high fat diet, coffee, alcohol, and cigarette smoking. If early satiety, postprandial bloating, or nausea is dominant, taking six small low fat meals per day may help decrease the intensity of the symptoms. However, none of these interventions is of established value.

Although antacids are commonly taken by patients with dyspepsia, double blind controlled trials have shown they are not superior to placebo in functional dyspepsia.[26] H_2 receptor antagonists are widely prescribed for dyspeptic patients, but double blind controlled trials have reported mixed results[24]; other data suggest that responders to H_2 blockers may be restricted to a subset with unrecognized GERD.[27] A meta-analysis has suggested a therapeutic gain of approximately 20% over placebo, which is comparable with the response obtained with prokinetics.[24]

Proton pump inhibitors seem to be modestly superior to placebo in functional dyspepsia, but patients with dysmotility-like dyspepsia do not respond.[13] In contrast, prokinetics have generally been found to be superior to placebo, although negative findings have also been published.[22 24]

Erythromycin is a macrolide antibiotic with prokinetic properties, but its side effects and rapid tachyphylaxis limit its clinical utility.[26] Visceral analgesics (e.g., fedotozine), antispas-

modics (e.g., trimebutine), antinauseants (e.g., ondansetron), antidepressants (e.g., amitryptiline), and *H pylori* eradication have also been tested in functional dyspepsia but are not of established benefit.[26 28 29] Little is known about the efficacy of behavioral therapy.

Choice of drug therapy

It seems logical to individualize drug therapy in functional dyspepsia. The committee believes that it is acceptable in general to consider an antisecretory or a prokinetic agent as first-line treatment for the patient with ulcer-like and dysmotility-like dyspepsia, respectively. Intermittent treatment courses (e.g., 2–4 weeks) may be considered when symptoms significantly impact on the patient's quality of life. In the rare patient whose symptoms are unremitting and incapacitating in the absence of medication, continuous therapy may be required. This approach needs appropriate testing in community trials.

There is evidence that symptoms in most patients with *H pylori* positive functional dyspepsia do not improve with eradication of the organism.[28 29] The physician faced with the problem of a patient with functional dyspepsia who wishes to prescribe eradication therapy should proceed to treatment only after explaining to the patient that there can be no confident expectation of symptomatic benefit and that there is a small risk of adverse reactions.

B2. Aerophagia

DEFINITION

Aerophagia is an unusual presenting complaint. It refers to a repetitive pattern of swallowing or ingesting air and belching. It is usually an unconscious act unrelated to meals, and is presumably a learned habit.

DIAGNOSTIC CRITERIA

At least 12 weeks, which need not be consecutive, in the preceding 12 months of:

(1) Air swallowing that is objectively observed, and

(2) Troublesome repetitive belching.

RATIONALE FOR CHANGES IN DIAGNOSTIC CRITERIA

The committee concluded, based on strong clinical impressions, that aerophagia cannot be firmly diagnosed without observation of the occurrence of excessive air swallowing. As belching is a normal phenomenon, the committee concluded that the symptom must be troublesome to be clinically relevant. Bloating or other symptoms that are part of discomfort may temporarily benefit from belching in these patients. As visible abdominal distension is often part of the IBS rather than a gastroduodenal disorder, and as belching may not reduce distension, a requirement that belching relieves visible distension was considered unlikely to be of value.

CLINICAL EVALUATION

A positive diagnosis is based on a careful history and observation of air swallowing. In typical cases no investigation is required. Patients with GERD have increased air swallowing, but this is usually clearcut clinically. It is important to screen for psychiatric disease, including depression and anxiety.

TREATMENT

Explanation of the symptoms and reassurance are important. The habit can sometimes be unlearned by demonstrating chest expansion and air ingestion as the patient belches. Treatment of associated psychiatric disease or use of stress reduction techniques may be worth considering.

Dietary modification (avoiding sucking hard candies or chewing gum, eating slowly and encouraging small swallows at mealtime, and avoiding carbonated beverages) is often recommended, but has not been rigorously tested and is usually disappointing in practice.

Although tranquilizers may occasionally be useful in severe cases,[30] drug therapy is not generally recommended. The value of psychologic interventions is essentially unknown.

B3. Functional vomiting

DEFINITION

Nausea is a subjective symptom that most people describe as a queasy, sick to the stomach sensation that may progress to the sense of a need to vomit. Vomiting is the forceful expulsion of gastric contents from the stomach. In functional vomiting, recurrent vomiting is the main presenting complaint and all known medical and psychiatric causes for the problem have been excluded.

DIAGNOSTIC CRITERIA

At least 12 weeks, which need not be consecutive, in the preceding 12 months of:

(1) Frequent episodes of vomiting, occurring on at least three separate days in a week, and

(2) Absence of criteria for an eating disorder, rumination, or major psychiatric disease according to DSM-IV, and

(3) Absence of self-induced and medication-induced vomiting, and

(4) Absence of abnormalities in the gut or central nervous system, and metabolic diseases to explain the recurrent vomiting.

A working definition of frequent episodes of vomiting adopted by the committee is at least one vomiting episode on three separate days in a week. This definition requires validation. The term psychogenic vomiting has no standard definition in the literature. The committee recommends that its use be abandoned in favor of functional vomiting as defined above.

CLINICAL EVALUATION

Functional vomiting is a rare condition in clinical practice. It should be distinguished from vomiting that occurs occasionally in patients with functional dyspepsia. The differential diagnosis of vomiting is extensive. Drugs should be excluded. It is important to rule out

mechanical obstruction of the gastrointestinal tract and central nervous system disease. Initial relevant tests include an upper endoscopy and small bowel radiography. A metabolic screen is essential to exclude electrolyte and other abnormalities. A computed tomography or ultrasound scan of the abdomen may also be indicated to exclude other intra-abdominal disease depending on the clinical setting. If these tests are normal, then an assessment of gastric neuromuscular function (e.g., gastric emptying) is required. Gastroduodenal manometry is useful to exclude a myopathic or neuropathic process, and can help to identify a missed obstructive disorder of the intestine. The EGG may be helpful when combined with gastric emptying assessment to evaluate otherwise unexplained vomiting.[31] Vomiting can occasionally be an atypical presentation of GERD which requires 24 hour esophageal pH testing to detect.[32] Autonomic function testing, if abnormal, may point to a central nervous system process which may be confirmed by a magnetic resonance image of the brain. Psychiatric disease as the primary cause also needs to be excluded. Vomiting needs to be distinguished from rumination, where there is effortless regurgitation of undigested food during or after every meal; the patient spits out or reswallows the food, which is not sour or bitter.[33] This syndrome is fully discussed in the chapter on the functional esophageal disorders.[34]

TREATMENT

Assessment of nutritional status is vital and appropriate intervention provided if there is a need. Antinauseants are worth a trial but are not of established value. Anecdotally, antidepressants can be of helpful in full doses. Psychosocial support is important. Behavioral and psychotherapy have not been adequately tested but may be considered.

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Rome III

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Functional Gastroduodenal Disorders

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A numerically important group of patients with functional gastrointestinal disorders have chronic symptoms that can be attributed to the gastroduodenal region. Based on the consensus opinion of an international panel of clinical investigators who reviewed the available evidence, a classification of the functional gastroduodenal disorders is proposed. Four categories of functional gastroduodenal disorders are distinguished. The first category, functional dyspepsia, groups patients with symptoms thought to originate from the gastroduodenal region, specifically epigastric pain or burning, postprandial fullness, or early satiation. Based on recent evidence and clinical experience, a subgroup classification is proposed for postprandial distress syndrome (early satiation or postprandial fullness) and epigastric pain syndrome (pain or burning in the epigastrium). The second category, belching disorders, comprises aerophagia (troublesome repetitive belching with observed excessive air swallowing) and unspecified belching (no evidence of excessive air swallowing). The third category, nausea and vomiting disorders, comprises chronic idiopathic nausea (frequent bothersome nausea without vomiting), functional vomiting (recurrent vomiting in the absence of self-induced vomiting, or underlying eating disorders, metabolic disorders, drug intake, or psychiatric or central nervous system disorders), and cyclic vomiting syndrome (stereotypical episodes of vomiting with vomiting-free intervals). The rumination syndrome is a fourth category of functional gastroduodenal disorder characterized by effortless regurgitation of recently ingested food into the mouth followed by rechewing and reswallowing or expulsion. The proposed classification requires further research and careful validation but the criteria should be of value for clinical practice; for epidemiological, pathophysiological, and clinical management studies; and for drug development.

A large group of patients with functional gastrointestinal disorders have chronic symptoms that can be attributed to the gastroduodenal region (Table 1). Based on the consensus opinion of an international panel of clinical investigators who reviewed the available evidence, a classification of the functional gastroduodenal disorders into functional dyspepsia (FD) (category B1, comprising postprandial distress syndrome [PDS] and epigastric pain syndrome [EPS]), belching disorders (category B2, comprising aerophagia and unspecified belching), functional nausea and vomiting disorders (category B3, comprising chronic idiopathic nausea [CIN], functional vomiting, and cyclic vomiting syndrome [CVS]), and the rumination syndrome (category B4) is recommended.

B1. Functional Dyspepsia

Definition of Functional Dyspepsia

Many different sets of symptoms have been used synonymously with the term dyspepsia, which has caused confusion. Most patients do not recognize the term dyspepsia, and historically physicians have interpreted the meaning of dyspepsia very variably.

Hence, the committee recommended the following pragmatic definition: FD is defined as the presence of symptoms thought to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms. These symptoms are listed in Table 2. However, particularly for experimental purposes, the term functional dyspepsia should preferably be replaced by more distinctively defined disorders, for which there is now increasing evidence in the literature. These are the new diagnostic categories of (1) meal-induced dyspeptic symptoms (PDS), and (2) epigastric pain (EPS).

Patients with 1 or more of these symptoms (postprandial fullness, early satiation, or epigastric pain or burning) are referred to as patients with dyspepsia. Previous Rome committees defined dyspepsia as pain or discom-

Abbreviations used in this paper: CIN, chronic idiopathic nausea; EPS, epigastric pain syndrome; FD, functional dyspepsia; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal antiinflammatory drugs; PDS, postprandial distress syndrome; PPI, proton pump inhibitor.

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Table 1. Functional Gastrointestinal Disorders

B. Functional gastroduodenal disorders
B1. Functional dyspepsia
B1a. Postprandial distress syndrome
B1b. Epigastric pain syndrome
B2. Belching disorders
B2a. Aerophagia
B2b. Unspecified excessive belching
B3. Nausea and vomiting disorders
B3a. Chronic idiopathic nausea
B3b. Functional vomiting
B3c. Cyclic vomiting syndrome
B4. Rumination syndrome in adults

fort centered in the upper abdomen and excluded reflux symptoms.[1] However, it has remained unsettled whether discomfort is a mild variant of pain or a separate symptom complex.[1,2] Moreover, discomfort comprised a large number of nonpainful symptoms including upper abdominal fullness, early satiety, bloating, or nausea. Bloating is an unpleasant sensation of tightness and should be distinguished from visible distention; usually, this symptom is not well localized and often occurs in IBS so bloating was not considered a cardinal symptom of dyspepsia. Nausea (queasiness or sick sensation or a feeling of the need to vomit) may occur with dyspepsia or IBS but is often from central origin and is also not considered a localizing symptom.[1–4] Whether or not individual symptoms such as upper abdominal fullness or bloating are labeled as pain by the patient may depend on cultural and linguistic factors and possibly education level.[2]

Heartburn has been defined by the esophageal committee. A burning sensation confined to the epigastrium is not considered to be heartburn unless it also radiates retrosternally. In the past, heartburn (as well as acid regurgitation) has often been included as sufficient on its own to define dyspepsia.[3] Heartburn is not considered a symptom that primarily arises from the gastroduodenum, and there is evidence that heartburn has moderate specificity for gastroesophageal reflux disease (GERD).[4,5] Hence, the committee concluded that heartburn is excluded from the definition of dyspepsia even though it may occur simultaneously with gastroduodenal symptoms. Similarly, retrosternal pain suggestive of esophageal disease or of a type embraced by the term noncardiac chest pain is excluded from dyspepsia.

Uninvestigated versus investigated dyspepsia. Especially when considering epidemiological data, it is important to distinguish the subjects with dyspeptic symptoms who have not been investigated from patients with a diagnostic label after investigation, with or without an identified causal abnormality.

Organic versus idiopathic dyspepsia. From an etiological viewpoint, patients with dyspeptic symptoms can be subdivided into 2 main categories:

1. Those with an identified organic or metabolic cause for the symptoms where, if the disease improves or is eliminated, symptoms also improve or resolve (eg, peptic ulcer disease, GERD with or without esophagitis, malignancy, pancreaticobiliary disease, or medication use).
2. Those with no identifiable explanation for the symptoms. In some of these patients, an identifiable pathophysiological or microbiologic abnormality of uncertain clinical relevance (eg, *Helicobacter pylori* gastritis) may be present, which is not thought to explain the symptoms. Others have abnormal motor or sensory dysfunction (eg, altered gastric emptying, fundic dysaccommodation, or gastroduodenal hypersensitivity) of uncertain significance. This broad group of patients with idiopathic dyspepsia has previously been referred to as nonulcer dyspepsia, essential dyspepsia, idiopathic dyspepsia, or FD. FD is currently the most recognized term in the literature.

Epidemiology

Approximately 20% to 30% of people in the community each year report chronic or recurrent dyspeptic symptoms.[6,7] Although these data represent uninvestigated dyspepsia and often also included heartburn, an organic cause is found in only a minority of dyspeptic subjects who

Table 2. Dyspeptic symptoms and their definitions

Symptom	Definition
Epigastric pain	Epigastric refers to the region between the umbilicus and lower end of the sternum, and marked by the midclavicular lines. Pain refers to a subjective, unpleasant sensation; some patients may feel that tissue damage is occurring. Other symptoms may be extremely bothersome without being interpreted by the patient as pain.
Epigastric burning	Epigastric refers to the region between the umbilicus and lower end of the sternum, and marked by the midclavicular lines. Burning refers to an unpleasant subjective sensation of heat.
Postprandial fullness	An unpleasant sensation like the prolonged persistence of food in the stomach
Early satiation	A feeling that the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal being eaten, so that the meal cannot be finished. Previously, the term "early satiety" was used, but satiation is the correct term for the disappearance of the sensation of appetite during food ingestion.

are investigated, and hence it is reasonable to assume that the majority would have functional dyspepsia.[8,9] Based on prospective studies of subjects who report dyspeptic symptoms for the first time, the incidence is approximately 1% per year.[7,10] The majority of patients with unexplained dyspeptic symptoms continue to be symptomatic over the long-term despite periods of remission.[11] Approximately, 1 in 2 subjects is estimated to seek health care for their dyspeptic symptoms at some time in their life.[12] Pain severity and anxiety (including fear of serious disease) appear to be factors associated with consulting behavior.[12,13]

Heterogeneity of FD Symptoms: Subgroups

It seems likely that chronic unexplained dyspepsia includes different types of patients with distinct underlying pathophysiologies who require different management approaches. However, it has been particularly difficult to identify these subgroups reliably. Subclasses based on symptom clusters have been proposed.[6,14] In clinical practice, however, this classification showed great overlap between subclasses, limiting its value.[7,15]

Identifying the predominant symptom was shown to distinguish subgroups with different demographic and symptomatic properties and with some relationship to putative pathophysiological mechanisms like delayed gastric emptying and presence of *H pylori*.[15] Thus, the Rome II committee proposed a subdivision according to the predominant symptom being pain or discomfort, but this subdivision has also been criticized because of the difficulty distinguishing pain from discomfort, the lack of an accepted definition of the term predominant, number of patients who do not fit into one of the subgroups, and especially the lack of stability, even over short time periods.[4,7,16]

A different approach was based on attempts to identify pathophysiology-based subgroups. Thus, associations were shown between symptom patterns and delayed gastric emptying,[17–19] impaired fundic accommodation,[20] and visceral hypersensitivity.[21] However, the association of these pathophysiological mechanisms with symptoms has not been confirmed in other studies.[22–24]

Diagnostic Criteria

The committee proposed to define FD at 2 levels. A general, more umbrella definition of FD, to be used mainly for clinical purposes, and although further research on more specific definitions is ongoing, is provided under category B1. However, particularly for pathophysiological and therapeutic research purposes, newly defined entities of (1) meal-induced dyspeptic symptoms (PDS, defined under category B1a), and (2) epigastric pain (EPS, defined under category B1b), should be used operatively.

B1. Diagnostic Criteria* for Functional Dyspepsia

Must include

1. *One or more* of:
   a. Bothersome postprandial fullness
   b. Early satiation
   c. Epigastric pain
   d. Epigastric burning

   AND
2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

B1a. Diagnostic Criteria* for Postprandial Distress Syndrome

Must include *one or both* of the following:

1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week
2. Early satiation that prevents finishing a regular meal, at least several times per week

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

Supportive criteria

1. Upper abdominal bloating or postprandial nausea or excessive belching can be present
2. EPS may coexist

B1b. Diagnostic Criteria* for Epigastric Pain Syndrome

Must include *all* of the following:

1. Pain or burning localized to the epigastrium of at least moderate severity at least once per week
2. The pain is intermittent
3. Not generalized or localized to other abdominal or chest regions
4. Not relieved by defecation or passage of flatus
5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

Supportive criteria

1. The pain may be of a burning quality but without a retrosternal component
2. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting
3. Postprandial distress syndrome may coexist

Overlap with GERD and IBS. Heartburn, considered an esophageal symptom, as well as dyspepsia are extremely common, and some overlap between both is likely. The Rome II definition proposed to exclude patients with predominant heartburn from the dyspepsia spectrum,[1] but recent studies have shown that the predominant symptom approach does not reliably identify all patients with GERD.[23–28] In general, overlap of GERD with PDS or EPS is probably frequent and needs to be carefully considered in both clinical practice and experimental trials. The committee recommends that the presence of frequent and typical reflux symptoms should lead to a provisional diagnosis of GERD.[29] In clinical practice and for clinical trials, recognition of frequent heartburn may be improved by a simple descriptive questionnaire.[26,27] The presence of heartburn does not exclude a diagnosis of PDS or EPS if dyspepsia persists despite a trial of adequate acid suppression therapy.

Overlap between dyspeptic symptoms and IBS is also commonly observed, and overlap between IBS on one hand and PDS or EPS on the other hand is likely to occur. The presence of IBS does not exclude the diagnosis of any of these functional gastroduodenal disorders because coexisting IBS was found to have a minor impact on symptom pattern and putative pathophysiological mechanisms in FD.[30]

Rationale for Changes in Criteria From Rome II

The rationale for the proposed new classification was based on the inadequacy of prior approaches such as the predominant symptom, the results of factor analysis in tertiary care and in the general population, clinical experience, and new observations in the peer-reviewed literature. Previously, all patients without definite structural or biochemical explanation for dyspeptic symptoms were considered to have functional dyspepsia. The committee agreed that there is a lack of uniform interpretation and acceptance of the term FD at different levels of practice, in different countries and with regulatory authorities. Despite the Rome II recommendations, several recent large studies included heartburn and even acid regurgitation as "typical symptoms of dyspepsia."[25,28,31]

There is also increasing evidence for the existence of different entities within the "dyspepsia symptom complex." There is no single symptom that is present in all patients with FD, and there is considerable variation in the symptom pattern between patients.[32] Factor analysis studies in the general population and in patients with idiopathic dyspeptic symptoms[7,33–40] have failed to support the existence of FD as a homogeneous condition. Pathophysiological studies have provided evidence for heterogeneity of putative underlying pathophysiological mechanisms, and the association of symptoms with mechanisms is better for certain symptoms than for the overall dyspepsia symptom complex.[17–21,32] Moreover, there is evidence for different response to therapy for different subgroups in therapeutic studies in functional dyspepsia.[28,31]

In clinical practice, in the absence of medication approved for functional dyspepsia, therapy is usually directed toward individual symptoms (eg, symptomatic treatment of nausea), rather than the full symptom complex. In many clinical trials, different therapeutic responses for different symptoms seem expected because strategies are used to enrich the patient population for certain symptom profiles.[31,41–43] Based on these limitations, the committee proposes to focus the notion of FD into more distinctively defined disorders.

Factor analysis studies in the general population and in patients with idiopathic dyspeptic symptoms generally conclude that dyspeptic symptoms comprise 3 or 4 different symptom groupings[33–40] (Table 3). By definition, certain symptoms such as early satiation or postprandial fullness are related to the ingestion of a meal. The factor analysis studies have uniformly identified a separate factor of meal-related symptoms.[7,33–40] Systematic studies revealed that symptoms are induced or worsened by meal ingestion in the majority of, but not all, patients with dyspeptic symptoms.[37,44] The committee considers a distinction between meal-induced symptoms and meal-unrelated symptoms to be both pathophysiologically and clinically relevant. Other consistently found symptom groupings include an epigastric pain factor and a nausea factor (with or without vomiting)[33–40] (Table 3). In some studies, belching also appears as a separate symptom group.[34,38]

Clinical Evaluation

The management of the patient with uninvestigated dyspeptic symptoms should not be confused with the approach to the patient whose dyspepsia has been investigated.

Patients With Uninvestigated Dyspeptic Symptoms

Evidence-based analysis[45] suggests the following 6-point management strategy for primary care physicians first seeing patients with dyspepsia:

1. Gather clinical evidence that symptoms most likely arise in the upper gastrointestinal tract.
2. Exclude alarm features (eg, unexplained weight loss, recurrent vomiting, progressive dysphagia, and gas-

Table 3. Factor Analysis Studies of Dyspeptic Symptoms in the General Population and in Tertiary Care Functional Dyspepsia Patients

Study	Setting	Symptom groupings
Westbrook, 2002[55]	Dyspepsia questionnaire in random population sample (n = 2300)	3 dyspeptic symptom factors: an epigastric pain factor, an early satiation/postprandial fullness factor, and a nausea factor. In addition, a heartburn/regurgitation factor
Fischler, 2003[56]	Dyspepsia questionnaire in 438 tertiary care patients with idiopathic dyspeptic symptoms	4 dyspeptic symptom factors: an epigastric pain factor, a postprandial fullness/bloating factor, a nausea/vomiting/satiation factor, and a belching factor
Tack, 2003[57]	Dyspepsia questionnaire in 636 tertiary care patients with idiopathic dyspeptic symptoms	3 dyspeptic symptom factors: an epigastric pain/burning/belching factor, a postprandial fullness/bloating/early satiation factor, and a nausea/vomiting/satiation factor
Jones, 2003[58]	Dyspepsia questionnaire in random population sample (n = 888)	3 dyspeptic symptom factors: an epigastric pain factor, a postprandial fullness/early satiation factor, and a nausea/vomiting factor
Kwan, 2003[59]	Rome II questionnaire in 1012 functional gastrointestinal patients	3 dyspeptic symptom factors: an epigastric pain/discomfort factor, a postprandial fullness/early satiation/bloating factor, and a nausea/vomiting factor
Whitehead, 2003[60]	Rome II questionnaire in 1041 functional gastrointestinal patients	4 dyspeptic symptom factors: 2 epigastric pain factors, a nausea/vomiting/early satiation factor, and an upper abdominal bloating factor
Camilleri, 2005[61]	Telephone survey in random population US sample (n = 21,128)	3 dyspeptic symptom factors: an epigastric pain/bloating/postprandial fullness factor, an early satiation/postprandial fullness/loss of appetite factor, and a nausea factor. In addition, a heartburn/regurgitation factor
Piessevaux, 2005[62]	Face-to-face interview of general population sample (n = 2025)	4 dyspeptic symptom factors: an epigastric pain factor, a postprandial fullness/early satiation factor, a nausea factor, and a belching factor

trointestinal blood loss), which are less common in general practice and which have a low positive predictive value for organic disease when present but which should still prompt investigation to exclude serious disease.[29,46]

3. Exclude ingestion of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs).[47]
4. In the presence of typical reflux symptoms, a provisional diagnosis of GERD should be made.[29] Physicians may initially prescribe proton pump inhibitors (PPIs) empirically in patients who also have heartburn but should take into account that these drugs may be less effective in FD without heartburn.[25,28] If EPS or PDS symptoms persist despite an adequate PPI trial, GERD is an unlikely explanation.
5. Noninvasive testing of *H pylori* infection, followed by eradication ("test and treat") is a cost-effective approach that decreases the number of endoscopies.[48–51] This strategy is indicated for the patient with no alarm features.[52] Test and treat is recommended as this strategy will cure most underlying peptic ulcer disease and prevent future gastroduodenal disease, although many infected patients with functional dyspepsia will not gain symptomatic benefit.[53,54] In those who fail treatment despite Hp eradication, a trial of PPI therapy is a reasonable next step. The yield of this approach is therefore highest in places with a high prevalence of *H pylori*–related peptic ulcer disease. Test and treat effectiveness decreases in case of a low prevalence, which makes false-positive testing more likely.
6. Prompt endoscopy is recommended in patients with alarm symptoms or patients over a threshold age (45–55 years, depending on health care access and incidence of malignant disease). Current evidence indicates that endoscopy first may be more cost-effective in older patients, that Hp testing followed by endoscopy in Hp-positive patients may not be cost-effective, and that many patients with negative *H pylori* tests will still need to undergo endoscopy because of alarm features or age.[55,56]

Patients With Functional Dyspepsia

The available data in the literature are based on functional dyspepsia; no data are available on diagnostic approaches to the categories EPS or PDS as defined by the Rome III committee. Performance of an upper endoscopy during a symptomatic period off acid-suppressant therapy is essential to identify functional dyspepsia appropriately by excluding other important structural diseases. It is recommended that biopsies be routinely obtained at the time of endoscopy to detect *H pylori* infection and, in view of the association of *H pylori* with peptic ulcer disease and dyspepsia, eradication is recommended in all positive cases.[53,54,57]

A barium meal study is less sensitive and specific than upper endoscopy, and hence it is not generally recommended. Ultrasonography is not recommended as a routine clinical test because the yield is low in the absence of symptoms or clinical features or biochemical tests suggestive of biliary tract or pancreatic disease.[58] Barium x-ray study of the small bowel is only useful in case of suspected mechanical obstruction.

A gastric-emptying study (eg, scintigraphy, ^{13}C-octanoic acid, or ultrasonography) is not currently recommended as a routine clinical test because the results uncommonly alter management. Recent studies have shown that less than 25% of patients with FD have delayed gastric emptying, even when considering exclusively the Rome II subgroup of dysmotility-like dyspepsia.[19,24,31] Inconsistent correlations have been shown between symptoms and abnormalities of gastric function assessed by gastric barostat or electrogastrography.[31] None of these tests can be advocated in routine clinical practice.

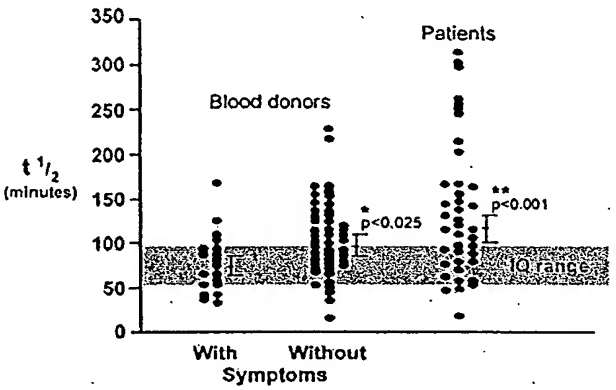

Figure 1. Prevalence of gastric emptying in the community: blood donors without and with dyspepsia, and patients with documented functional dyspepsia. Gastric emptying was significantly slower in healthy blood donors with symptoms versus those without, and was slower in patients with functional dyspepsia compared with healthy asymptomatic blood donors. (Reprinted from Haag et al. Gut 2004; 53:1445–1451).

Physiologic Features

The available data in the literature are based on FD patients as a group; no data are available on the physiological features of the categories EPS or PDS as newly defined by the Rome III committee.

Little is known about the influence of nutrient intake in the etiology of FD.[59] Neither smoking, alcohol, or NSAIDs are considered to be risk factors for FD.[60] However, patients with FD are more likely to develop symptoms when treated with NSAIDs.[61] Basal gastric acid secretion is within normal limits in patients with FD,[62] but acid-related symptoms (perhaps through gastric or duodenal hypersensitivity, see later) may arise in a subgroup of patients.

The role of *H pylori* infection in FD has been controversial, but recent meta-analyses suggest a small benefit from *H pylori* eradication in infected patients. No consistent disturbances of motor or sensory function of the upper gut have been reported in *H pylori*–infected individuals.[32,63]

There are several lines of evidence that gastrointestinal motility is abnormal in a proportion of patients with FD. The contribution of motor abnormalities to symptom generation is incompletely established. Impaired (typically delayed) gastric emptying of solids is the most widely studied motility disorder in dyspepsia.[32] Figure 1 shows that gastric emptying is slower in patients with FD compared with healthy controls. The delay in gastric emptying may be more common among patients with fullness, nausea, and vomiting and in females, but this is controversial.[17–19,32] Several studies show that the accommodation or volume response of the stomach after a meal is reduced in ~40% of patients with functional dyspepsia.[20,32] Other disturbances of upper gut motility are postprandial antral hypomotility,[32,64] reduced frequency of interdigestive migrating motor complexes,[65] impaired duodenal motor responses to acid and nutrient infusion,[66] and excess of phasic contractions of the fundus after the meal.[67] Several studies have documented the presence of gastric dysrhythmias especially in the postprandial period in patients with FD.[33,68]

Evidence of gastric hypersensitivity in a subset of functional dyspepsia is well documented in the literature.[21,32,69] The brain centers involved in sensation of gastric stimuli like distention have been documented in health,[70,71] and full reports of the brain centers involved in functional dyspepsia are awaited. Altered intestinal sensitivity has been observed in response to balloon distention or in response to duodenal acid or lipid infusion.[72–74] A subset of dyspeptic patients has spontaneously increased duodenal acid exposure, and this is associated with higher symptom intensity.[75] The role of altered parasympathetic and sympathetic activity, of altered secretion of gastrointestinal hormones, and of G-protein polymorphisms requires further study.[63,76,77]

Psychological Features

In dyspepsia, there is evidence of an association with psychopathological factors, and comorbidity with psychiatric disorders, especially anxiety disorders, is high.[12,13,32,78,79] It is still unclear whether these psychopathological factors determine health care–seeking behavior, whether they play a key role in the pathophysiology of the dyspepsia symptom complex, or whether they reflect a common predisposition for functional and psychological disorders. Abnormalities of several psychosocial dimensions were found to be associated

with epigastric pain and with hypersensitivity to gastric distention in FD.[34]

Treatment

The available data in the literature apply to FD patients as a group; no data are available on treatment approaches to the categories EPS or PDS as newly defined by the Rome III committee. Evaluation of pharmacotherapy in FD is confounded by high placebo response rates from 20% to 60%.[80] Reassurance and explanation represent the first management step and may be sufficient in many patients. Stopping smoking and ceasing consumption of coffee, alcohol, or NSAIDs is commonly recommended, but there is no convincing evidence of efficacy.[60] Although it seems plausible to recommend taking several small low-fat meals per day, this has not been formally investigated.

Acid suppression is safe and remains first-line therapy in the absence of *H pylori* infection; an adequate trial of therapy should be given and stepped up if unsuccessful initially. Patients with dyspepsia often take antacids, although there is no proof of efficacy.[81] A Cochrane meta-analysis evaluating the efficacy of H_2-receptor antagonists in functional dyspepsia reported a significant benefit over placebo with a number needed to treat of 8.[82] However, these trials were relatively small and heterogeneous and often misclassified reflux disease as functional dyspepsia, which may account for much of the benefit. A meta-analysis of controlled, randomized trials with PPIs in functional dyspepsia reported that this class of agents was superior to placebo with a number needed to treat of 7.[83] Much of this benefit may be explained by unrecognized GERD.[26,31,83] Furthermore, epigastric pain, but not meal-related symptoms, seems to respond to a PPI.[28,31,83] There is no evidence that high-dose PPI therapy is beneficial over standard dosing, but an empiric trial of high-dose PPI in practice may be considered in difficult cases.

A Cochrane meta-analysis reported an 8% pooled relative-risk reduction with eradication of *H pylori* compared with placebo at 12 months of follow-up.[53] The number needed to treat was calculated to be 17. Because *H pylori* eradication can induce sustained remission in a small minority of patients, this should be routinely considered once the benefit and risks have been carefully discussed with the patient.

Gastroprokinetic drugs like metoclopramide, domperidone, and cisapride appear efficacious in functional dyspepsia compared with placebo but have been poorly studied.[82,84] Publication bias may also account in part for some of the positive meta-analyses in the literature.[82] Cisapride has been withdrawn from most markets in the world because of rare fatal arrhythmias. The macrolide antibiotic erythromycin acts on the motilin receptor to increase gastric emptying rate in patients with diabetic and idiopathic gastroparesis,[85,86] but its side effects and tachyphylaxis limit its clinical utility. ABT-229, a synthetic motilin-like prokinetic drug without antibacterial activity, was of no significant benefit in functional dyspepsia over placebo, possibly because the drug impairs fundic relaxation.[41] Several other approaches to FD, including fundus-relaxing drugs, new prokinetics, selective serotonin reuptake inhibitors, and visceral analgesic drugs are currently under investigation.[87–89]

The value of antidepressants in FD is not established. In 1 crossover trial of 7 patients, amitryptiline in low doses improved symptoms but not visceral hypersensitivity or sleep.[90] Limited promising data are available on psychotherapy or hypnotherapy,[91,92] but more studies are needed.

B2. Belching Disorders

Air swallowing during eating and drinking is a normal physiological event and so is venting of the ingested air during transient relaxations of the lower esophageal sphincter.[93] Hence, belching can only be considered a disorder when it becomes troublesome. The committee distinguishes aerophagia from unspecified excessive belching.

B2a. Diagnostic Criteria* for Aerophagia

Must include *all* of the following:

1. Troublesome repetitive belching at least several times a week
2. Air swallowing that is objectively observed or measured

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.*

B2b. Diagnostic Criteria* for Unspecified Excessive Belching

Must include *all* of the following:

1. Troublesome repetitive belching at least several times a week
2. No evidence that excessive air swallowing underlies the symptom

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.*

Justification for Changes to the Criteria

In the previous Rome II classification, aerophagia was described as an unusual disorder with excessive belching due to air swallowing. The committee decided

to expand the category based on consensus that excessive belching is a presenting symptom and based on recent evidence, obtained with intraluminal impedance measurement of air transport in the esophagus,[93] which confirms that different mechanisms of excessive belching occur.[94] Belching is usually an unconscious act, and the motility patterns of belching are quite similar to those found in gastroesophageal reflux.[93] A recent study performed by using intraluminal impedance measurement in aerophagia patients revealed swallowing of air that enters the esophagus very rapidly and is expulsed almost immediately in the oral direction.[94] This phenomenon of "supragastric belching," clearly distinct from "gastric" belching, is not accompanied by transient relaxation of the lower esophageal sphincter and is only observed in aerophagia.[94]

Clinical Evaluation

A positive diagnosis is based on a careful history and observation of air swallowing. In typical cases, no investigation is required. Excessive belching may also accompany GERD, and in difficult cases, pH monitoring or empirical acid suppressive therapy may be considered.[95] Belching is also often reported in dyspepsia in which it does not respond to acid suppressive therapy.[95] In FD, belching is associated with hypersensitivity to gastric distention,[21,32,34] which supports the concept that belching is induced to relieve upper abdominal discomfort. Rumination can usually be distinguished by the history and observation. It may be important to screen for psychiatric disease, but there is no evidence of excess psychopathology in aerophagia or in functional dyspepsia with symptoms of belching.[34]

Treatment

Explanation of the symptoms and reassurance are important. The habit can sometimes be inhibited by showing chest expansion and air ingestion as the patient belches. Dietary modification (avoiding sucking candies or chewing gum, eating slowly and encouraging small swallows, and avoiding carbonated beverages) is often recommended but has not been rigorously tested. Behavioral therapy seems helpful in some cases, but clinical trials are lacking. Studies investigating drug therapy specifically in aerophagia are also lacking.

B3. Nausea and Vomiting Disorders

Definition

Nausea is a subjective symptom and can be defined as an unpleasant sensation of the imminent need to vomit typically experienced in the epigastrium or throat. Vomiting refers to the forceful oral expulsion of gastric or intestinal content associated with contraction of the abdominal and chest wall muscles. Vomiting must be distinguished from regurgitation and rumination.

B3a. Diagnostic Criteria* for Chronic Idiopathic Nausea

Must include *all* of the following:

1. Bothersome nausea, occurring at least several times per week
2. Not usually associated with vomiting
3. Absence of abnormalities at upper endoscopy or metabolic disease that explains the nausea

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

B3b. Diagnostic Criteria* for Functional Vomiting

Must include *all* of the following:

1. On average, 1 or more episodes of vomiting per week
2. Absence of criteria for an eating disorder, rumination, or major psychiatric disease according to DSM-IV
3. Absence of self-induced vomiting and chronic cannabinoid use and absence of abnormalities in the central nervous system or metabolic diseases to explain the recurrent vomiting

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

B3c. Diagnostic Criteria* for Cyclic Vomiting Syndrome

Must include *all* of the following:

1. Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)
2. Three or more discrete episodes in the prior year
3. Absence of nausea and vomiting between episodes

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

Supportive criterion

History or family history of migraine headaches.

Rationale for changes in criteria. After review of the available literature, a new category, CIN was added.

In the Rome II criteria, nausea was considered a symptom of motility-like dyspepsia,[1] but the committee decided to revise this on the basis of factor analysis data, on clinical experience that persistent nausea is often of central or psychological origin, and on the lack of responsiveness of this symptom to empiric therapy.

The committee slightly modified the previous definition of functional vomiting based on the setting of threshold frequencies and on the recognition of cannabinoid use as a mechanism. A new category, cyclical vomiting in adults, was added based on expert opinion and a better appreciation that those with stereotypical attacks of cyclical vomiting differ from those with functional vomiting.

Clinical Features

Nausea is a common symptom, and the differential diagnosis is wide. The committee recognized a group of patients exist who have frequent unexplained nausea with little or no vomiting. The mechanisms remain unknown.

In children, the syndrome of cyclical vomiting is well described (See "Childhood Functional Gastrointestinal Disorders: Neonate/Toddler" on page 1519 in this issue). Although it is rare, adults may develop cyclical vomiting in middle age, and both men and women are affected.[96,97] Only 1 in 4 adults had a history of migraine headaches. Adults have a mean of 4 cycles of vomiting per year, with a mean duration of 6 days (range, 1–21) and an average symptom-free interval of 3 months (range, 0.5–6).[96,97]

The mechanisms underlying functional and cyclic vomiting remain unknown. Major depression has been linked to habitual postprandial and irregular vomiting, whereas conversion disorder may explain some cases of continuous vomiting.[98] In cyclical vomiting in adults, psychiatric disease appears to be uncommon, with the largest adult series suggesting only 20% having anxiety or another psychiatric disorder.[98]

Clinical Evaluation

The differential diagnosis of recurrent nausea or vomiting is extensive. Many drugs, including cannabinoid use, may cause nausea and vomiting.[99,100] In patients with a history of "vomiting," rumination and eating disorders need to be excluded by careful clinical evaluation.

It is particularly important to exclude intestinal obstruction, gastroparesis, and intestinal pseudo-obstruction as well metabolic and central nervous system disease (eg, brainstem lesions on magnetic resonance imaging) in adults presenting with recurrent unexplained vomiting.[99] An upper endoscopy and a small bowel x-ray or computed tomography enterography are performed to exclude gastroduodenal disease and small bowel obstruction. Biochemical testing is also essential to exclude electrolyte abnormalities, hypercalcemia, hypothyroidism, and Addison's disease. If these tests are normal, then it is reasonable to consider gastric-emptying evaluation or gastrointestinal manometry. The use of electrogastography is not widely accepted, although gastric dysrhythmias may be recorded in some patients with unexplained nausea and vomiting with normal gastric emptying.[101]

Treatment

The treatment of chronic idiopathic nausea is not defined. Antinausea drugs provide limited benefit empirically. Commonly used antinauseants like prochlorperazine, diphenhydrinate, and cyclizine promethazine have not been systematically studied in unexplained nausea and have many side effects. Modest symptom improvement has been shown with the 5-hydroxytryptamine$_3$ antagonists ondansetron and alosetron over placebo in functional dyspepsia, but nausea has not been specifically studied.[42,89] Low-dose tricyclic antidepressant therapy may be helpful anecdotally.

In functional vomiting, management of nutritional status and psychosocial support is important. The role of dietary and pharmacological therapy, both frequently used, has not been specifically tested. There is also no evidence that medications are particularly useful in this group, although anecdotal reports suggest that tricyclic antidepressants are helpful.[97,100] Antiemetic drugs can be tried but are often of little value. Data are lacking on the value of behavioral or psychotherapy.

Patients with cyclical vomiting syndrome may require hospital admission and supportive care during severe bouts. Empiric treatments of antimigraine medications have been used with anecdotal reports of success, and a trial of antimigraine medications is worthwhile, especially when there is a family history of migraine headaches. There are anecdotal reports on the use of beta-blockers, tricyclic antidepressants, cyproheptadine, ketorolac, and several others.[96,97,102]

B4. Rumination Syndrome

Rumination syndrome is a condition characterized by the repetitive, effortless regurgitation of recently ingested food into the mouth followed by rechewing and reswallowing or expulsion.[103] Although initially described in infants and the developmentally disabled (reference to pediatric chapter), it is now widely recognized that rumination syndrome occurs in males and females of all ages and cognitive abilities.[103,104] In general, rumination is more common in females than males.

Epidemiology

The epidemiology of rumination syndrome in the adult general population remains to be carefully defined, but clinical impression suggests it is rare.

B4. Diagnostic Criteria* for Rumination Syndrome

Must include *both* of the following:

1. Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing
2. Regurgitation is not preceded by retching

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

Supportive criteria

1. Regurgitation events are usually not preceded by nausea
2. Cessation of the process when the regurgitated material becomes acidic
3. Regurgitant contains recognizable food with a pleasant taste

Clinical Evaluation

Rumination syndrome is a probably underappreciated condition in adults who are often misdiagnosed as having vomiting secondary to gastroparesis or gastroesophageal reflux or anorexia or bulimia nervosa. Clinical experience suggests that many individuals with rumination have additional symptoms including nausea, heartburn, abdominal discomfort, diarrhea, and/or constipation. Weight loss can also be a prominent feature of rumination syndrome, particularly in the adolescent population.[103,104] Typical clinical features include the following:

1. Repetitive regurgitation of gastric contents beginning within minutes of the start of a meal; this is to be contrasted with the typical history of vomiting in the later postprandial period in patients with gastroparesis.
2. Episodes often last 1–2 hours.
3. The regurgitant consists of partially recognizable food, which often has a pleasant taste according to the patients.
4. The regurgitation is effortless or preceded by a sensation of belching immediately before the regurgitation or arrival of food in the pharynx.
5. Regurgitation may be preceded by brisk voluntary contraction of the abdominis rectus.
6. There is usually lack of retching or nausea preceding the regurgitation.
7. Patients make a conscious decision regarding the regurgitant once it is present in the oropharynx. The choice may depend on the social situation at the time. Rumination is typically a "meal-in, meal-out, day-in, day-out" behavior.

An association between rumination and bulimia nervosa has been described,[105] although bulimic patients tend to expel rather than reswallow food and may self-induce vomiting. Pathophysiological mechanisms involved in rumination syndrome remain somewhat unclear, although all observations suggest some adaptation of the belch reflex that overcomes the resistance to retrograde flow provided by the lower esophageal sphincter.[105,106] Many patients have evidence of "pathological gastroesophageal reflux" because pH monitoring shows >4% time with intraesophageal pH below 4. However, careful study shows that this is typically in the first hour after a meal and that the time that esophageal pH is <4 may be paradoxically low because food buffers the gastric acid during the postprandial period when repetitive regurgitation occurs.

Treatment

Reassurance, explanation, and behavioral therapy are currently the mainstays of treatment in adolescents and adults of normal intelligence with rumination syndrome. PPIs are frequently used to suppress heartburn and to protect the esophageal mucosa while therapy is instituted. The preferred behavioral treatment for rumination syndrome consists of habit reversal by using diaphragmatic breathing techniques to compete with the urge to regurgitate.[107] Treatment of rumination in bulimics has been reported to be less successful.

Future Research

Rome III Definitions for Gastroduodenal Disorders

The relationship of the newly defined disorders (PDS, EPS, CIN, and CVS) to each other, to pathophysiological mechanisms, and to response to therapy needs to be assessed. The epidemiology of these disorders will also need to be studied carefully.

Mechanisms of Symptom Production

The goal should be that the field moves to therapy based on identified mechanisms. This requires more ex-

tensive understanding of the physiological mechanisms causing symptoms.

Diagnostic Issues

There is a great need for validated noninvasive diagnostic methods to help the clinician evaluate the etiology of symptoms and to target appropriate treatment. The pros and cons of the nutrient drink test need to be more thoroughly understood.

Therapeutic Issues

There is a need for further development of validated endpoints that may serve as biomarkers in the development of novel treatment approaches. Medications affecting the putative pathophysiological mechanisms require further development. Combination therapies need to be tested, to either enhance correction of underlying single pathophysiology, or to correct more than one pathophysiology. The peripheral and central effects of selective serotonin reuptake inhibitor, tricyclic antidepressants, and selective noradrenaline reuptake inhibitors in health and dyspepsia require thorough characterization. Appropriate pharmacoeconomic studies are also needed to test the true value of available and future therapies.

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